17-25 have been cancelled in accordance with this election to speed prosecution and without waiver of Dr. Sutcliffe's right to present these claims again in a further divisional application.

B. The Amendments

Claims 29 and 31 have been amended pursuant to the Examiner's helpful suggestions by deleting a redundant word and removing periods so that the claim had only one such punctuation mark.

C. Double Patenting Rejection

The pending claims have been rejected under the judicially-created doctrine of obviousness-double patenting over claims 1-3 of U.S. Patent No. 5,292,7998. A terminal disclaimer was helpfully noted as a way to overcome this rejection. This rejection is respectfully traversed.

The Action asserts that:

> "the method of determining amino acid residues are [sic] obvious over the DNA [of the present application]. Also in spite of the degeneracy of the genetic code, instant DNA can be obtained by employment of the peptides disclosed in the patented methods."

In In re Vogel, 164 USPQ 619 (CCPA 1970) relied-on in the Action, parent and continuation-in-part (CIP) applications were involved. The parent claimed a specific species and the CIP claimed the genus. Here, only one application is involved, with this application being a division of the relied-on U.S. Patent. It is therefore believed that an obviousness-type double patenting rejection based on Vogel is not appropriate here.

The last-quoted sentence above also cannot be agreed with. A claimed DNA must be complementary to a mammalian mRNA. It is submitted that knowing an amino acid residue sequence may not lead one to such a complementary DNA without undue experimentation. Thus, at the filing date here, knowing an amino

acid sequence would enable a skilled worker to prepare a DNA that would encode that sequence, but that DNA would not necessarily be complementary to a mammalian mRNA because PCR technology was not available until 1985 with publication of Saiki et al., Science, 239:487 (1985).

This basis for rejection should therefore be withdrawn.

D. Rejection Under 35 U.S.C. §112, Second Paragraph

All of the claims have been rejected as allegedly being vague and indefinite. Several bases are asserted for those conclusions, and those assertions will be dealt with below. This basis for rejection is respectfully traversed.

1. Extraneous Explanations Are Not Required

The Action asserts that:

> "The claims read on so many DNAs that one cannot determine which DNAs are intended. Moreover, it is not possible for the public to determine from the claims what they comprehend since they require explanations extraneous to both the specification and claims."

It can be agreed that the claims read on a large number of DNAs. Breadth is not, however, indefiniteness. See, for example, In re Gardner et al., 166 ASPQ 138 (CCPA 1970).

In regard to "explanations extraneous to both the specifications and claims", no explanation has been provided as to what explanations, extraneous or otherwise, are allegedly required by the claims. Rather, the claims are quite specific in that a claimed DNA complements an mRNA of a mammal, and that mRNA is present in brain cells of that mammal but not in the cells of the liver, kidney, gut, lung, heart or skeletal muscle of that mammal. These mRNAs are referred to as being brain-specific.

See page 14, lines 1-22. A brain-specific DNA also has a neuroactive function.

All of those recitations are in the claims. All of those recitations are supported in the specification as was noted in the Preliminary Amendment filed on October 10, 1994. This basis for rejection should therefore be withdrawn.

2. A Skilled Worker Would Readily Understand the Claim Language.

The Action next quotes from a claim as to the length of the DNA in bases and the nature of that DNA being complementary to a brain-specific mRNA. The Action asserts that the quoted language would not enable a skilled worker to determine the meaning intended by the quoted language. This assertion cannot be agreed with.

DNA length is usually measured by the number of bases in the chain. As a consequence, the recited length limitation is eminently clear to a worker of ordinary skill to whom these claims are directed.

Similarly, that a DNA is complementary to an RNA is the basis for Southern and Northern blotting techniques that are well known in this art and are discussed in the specifications. Again, a worker of ordinary skill would have no problem understanding this word, nor with cDNA as is claimed.

Cytoplasmic messenger RNA is what it says it is. That is, mRNA present in the cytoplasm of a cell as compared, for example to the nucleus or mitochondria. The skilled worker would also have no problem with that phrase.

The presence of the mRNAs in substantially only brain cells has been discussed in the parental applications. The Examiner's attention is also invited to page 28, lines 24-29. Here again, no problem in understanding should be encountered by a worker of ordinary skill with this phrase.

This basis for rejection should therefore be removed.

3. Definition of the Claimed Subject Matter is Clear to Those of Skill In This Art

The Action continued by asserting that the claimed "DNAs have not been defined by structure and the intended functions are unclear." Attention was directed to Ex parte Tanksley, 26 USPQ 2d 1384 (BPAI 1991) in which the Board held that the claims must be so definite as to allow their comparison with the available art and also to make it possible to determine from the claims what it is they comprehend.

The first of the Board's holdings appears to be correct, whereas the second does not appear to be the law inasmuch as the specification and prosecution file history should also be consulted by the "public" in determining what is comprehended by the claims. Nevertheless, it is submitted that the claims here are cast with sufficient clarity so that both tests are readily passed.

As to function of the DNAs, it is clear to a skilled worker that they are complementary to an mRNA that encodes a brain-specific proteinoid. The proteinoid is neuroactive. The function requested is thus asserted in the claims.

The structure of the DNAs need not be recited. The Board in Tanksley noted on reconsideration that one could claim the DNAs there in question by "base sequence...and/or function." Such a function has been asserted along with several base sequences. No more is needed under Tanksley.

To the question of whether a worker of ordinary skill could understand what is claimed here, one must remember that the present application contains almost all of two published papers that were made of record here and in each of the parent patents. Those two papers are Sutcliffe et al, Cell, 33:671-682 (1993) and Milner and Sutcliffe, Nucleic Acids Res., 11(6):5497-5520 (1983).

The claims are cast in the language of one or both of those papers, and as has been noted before, the words of those claims are readily understood by a worker of ordinary skill in this art. Those papers are so well understood that they have been cited about 380 times in the literature through February 15 of 1995, of which about 280 papers are by one or more authors that do not include Dr. Sutcliffe. That number of citations is clearly indicative of the fact that workers of ordinary skill know and understand what has been claimed here. A two-part photocopy of the printout from a citation search using the Dialog data base is enclosed as Exhibit 1.

It is thus submitted that not only does that "public" of skilled workers know what is comprehended by these claims, but that these claims can be compared with the prior art. Indeed, the Examiners of the two parental patents had little difficulty in comparing the polypeptides of U.S. Patent No. 4,900,911 encoded by a DNA claimed here with the art or the process steps of parental U.S. Patent No. 5,242,798 with the art.

The two tests of Tanksley have thus been passed. There is therefore no basis to limit the claims here only to the sequences originally disclosed. This rejection should therefore be withdrawn.

E. Rejection Under 35 U.S.C. §112, First Paragraph

All of the claims were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Action asserts that the "scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids broadly encompassed by the claims..." and that the number of DNAs claimed is indeterminant. This basis for rejection cannot be agreed with, and this rejection is respectfully traversed.

The enablement requirement as applied here requires that a worker of ordinary skill be able to make and use a cDNA of the claims. The Court has held that the question of enablement revolves around whether the

> "disclosure contains sufficient teaching regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" [In re Angstadt and Griffen, 190 USPQ 214, 218 (CCPA 1976); emphasis in the original.]

The Angstadt case dealt with a catalyst complex molecule that contained a transition metal cation from one of several Groups of the Periodic Table, an undisclosed "inorganic anion" for the metal cation, and a hexaalkylphosphoramide whose six alkyl groups contained one to thirty carbon atoms in each alkyl group. The metal salt (cation plus anion) was said to be present at 1-4 moles per molecule and the hexaalkylphosphoramide was present at 1-8 moles per molecule complex.

Footnote 2 of Angstadt noted that the Solicitor asserted that the claim read on thousands of compounds including "any one of at least 50 metal cations combined with any inorganic anion". Actually, "thousands" was a gross underestimate.

For example, there are eight C_1-C_4 alkyl groups; i.e., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and iso-butyl. So for the hexaalkylphosphoramidates where the alkyl groups are C_1-C_4, there are 8^6 or 262,144 different phosphoramidates, omitting possible chiral isomers. Multiplication by the number of cations, anions and ratios (1-4:1 salt and 1-8:1 hexaalkylphosphoramide per molecule) skyrockets the number of compounds just for that relatively small number of alkyl groups.

According to Noller, Chemistry of Organic Compounds, W.B. Saunders Company, Philadelphia, 1958, page 38, (Exhibit II enclosed here) there are over 4 billion C_{30} alkanes alone. Presuming the number of C_{30} alkyl groups is about the same as the

number of alkanes, which is a gross undervaluing as there are 15 straight chain C_{30} alkyls alone, the Angstadt formula actually therefore encompassed an astronomical number of separate compounds once all of the anion, cation, alkyl group and ratio permutations encompassed by the claims are taken into account. For example, there would be about $(4 \times 10^9)^6$ or (4096×10^{54}) different C_{30} hexaalkylphosphoramides alone. That number of compounds exceeds any arbitrarily large number that one could pick from the physical world such as the number of atoms in the earth if it were all iron [(mass = about 6×10^{27}g/55.6g/mole) X 6.023×10^{23} atoms/mole = about 6.5×10^{49} atoms] or the more chemically familiar Avagadro's Number of 6.023×10^{23} molecules per mole.

The Angstadt inventors disclosed just 40 examples, with one compound that did not work in their process. The Court there held that the inventors did not have to make and test every compound in their claims, nor did every compound have to work.

That Court went on to discuss the disclosure that there taught how to make and how to use a claimed catalyst. It continued that if a skilled worker wanted to make another catalyst than those specifically disclosed in the 40 examples that worker could simply follow the disclosure and make a desired catalyst compound. It further pointed out that the catalysis process was not complicated and needed no special conditions nor equipment. The Angstadt claims were found to be enabled despite the amazingly large number of catalysts encompassed.

That Court went further in saying that some "experimentation" was permitted and held that the key phrase was "undue", not "experimentation". Practicing of that invention "would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art' ... ", at 218 (citation omitted). The same should be the case here.

Angstadt dealt with synthetic organic chemistry. The present application deals with biochemistry.

Attention is invited to In re Wands, 8 USPQ2d 1400, 1407 (Fed.Cir. 1988), a case involving monoclonal antibody preparation and screening, biological and biochemical processes that are about as time consuming as the screenings required here. There, the Court found that practitioners of the art were prepared to screen negative hybridomas. A similar finding was made in Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed.Cir. 1986). Those familiar with the hybridoma/monoclonal antibody art know that such preparations and screenings often involve months to generate antibodies and thousands of assays. Those procedures are nevertheless well known, accepted and routine in the art.

Turning to the present application, the claims here encompass a large number of cDNAs. The specification teaches how to obtain a cDNA of the claims, as well as providing exemplary procedures.

It is submitted that many orders of magnitude fewer cDNAs are encompassed by the present claims than were encompassed by those found enabled in the Angstadt case. The biochemistry here is well known, straightforward and simple but require effort, no fancy equipment is needed here.

Thus, the number of species encompassed by a claim does not appear to be relevant. Rather, as the Court noted in In re Angstadt is whether the worker of ordinary skill is enabled by the disclosure to make and use the invention. The Action, using an unsubstantiated conclusion and a misplaced reliance on Ex parte Maizel, 27 USPC 2d 1662 (BPAI 1993) asserts that such a worker would not be properly enabled. The specification, Dr. Sutcliffe and other skilled workers through their publications that cite, rely-on and copy Dr. Sutcliffe's work disagree.

It is also submitted that the situation regarding the remaining, unsequenced clones of the application is analogous to that discussed in In re Wands, above. There, the inventors had prepared about 140 hybridomas, studied four within the claims and deposited one. The Board held the broad genus claims to those hybridomas/antibodies to not be enabled. The Court reversed.

Here, the brain-specific clones of the application such as those of Table III were shown to be within the claims as of the filing date. Their sequences have been published seriatim as determined over the last decade. Thus, Dr. Sutcliffe has gone further than did Wands et al. in their application and after an application was filed. The generic Wands materials were found to be enabled, and so should the brain-specific cDNAs here.

In determining who is a worker of ordinary skill in this art, it is appropriate to use the standard of Section 103, and determine the level of skill in this art at the time this invention was made. It is submitted that that level of skill was quite high. Thus, the worker of ordinary skill here would hold a Ph.D. or M.D. degree or both, and would have held a post-doctoral position for 2-4 years. That person would be a sole or senior author of at least six published book chapters, invited papers or other papers published in this field in refereed journals, and would be the head of her/his own research group, or would at least have several laboratory technicians, post-docs and/or graduate students reporting to her/him. Such a person would thus be directing, rather than just carrying out, work in this field.

The previously submitted papers (Documents CA, CB and CC of the IDS) provided views of such workers relating to the present invention and its lack of obviousness. Enclosed Documents DA, DB, DC and DD that are also noted on the enclosed Form PTO 1449 further attest to the enablement provided by the before-mentioned Milner and Sutcliffe, and Sutcliffe et al.

articles and thereby to the enablement provided by the present specification that includes the pertinent disclosures of those papers.

The Examiner's attention is first invited to Cimler et al., J. Biol. Chem., 262:12158-12163 (1987), Document DA. Those authors obtained brain-specific mRNA and prepared cDNA from that material. (See the Abstract, near the bottom.) Near the right-hand bottom of page 12162, those authors reviewed the Milner and Sutcliffe and Sutcliffe papers and classified their clone, P-57, into the brain-specific cDNAs of these claims; i.e., the Class III (Table III herein) materials.

Enclosed Document DB, Oyler et al., J. Cell. Biol., 109:3039-3052 (1989), describes a brain-specific protein called SNAP-25. Those authors recognized the present contribution in the second full paragraph of page 3040, along with contributions of others in the field. It should be noted that the cited Sutcliffe et al. paper, that is within this specification, has the earliest publication date by two years compared to the other papers as a means "to identify and characterize novel genes and their encoded proteins that are specifically expressed in the nervous system."

The Examiner's attention is next invited to the review of Document DC, Kato, TINS, 15:319-212 (1992). The paragraphs on page 321 under the heading "Shotgun analysis" are most compelling. The author here credits the Sutcliffe et al. paper included in this application as pioneering this field. That author then concluded the section of the review by stating:

> "Using the methods described above, rare clones of particular interest can be obtained. Unfortunately, a great deal of effort is required to obtain specific clones. However, the goal of making a reasonably

large catalogue of cDNAs is readily achievable."

A fourth paper, Document DD, Marechal et al., Anal. Biochem., 208:330-333 (1992) recognized the present contribution (footnote 3 to Milner and Sutcliffe) and disclosed a short cut involving a hybridization step that removed other than brain-specific clones. Nonetheless, the cDNA clones isolated contained 500 to about 2200 bp and corresponded to mRNAs that were not present in liver, kidney, spleen or intestinal (gut) tissues. Those clones were referred to as being brain-specific. (See the heading at page 332.)

The previous discussion and enclosed printout note that the two papers by Dr. Sutcliffe and his co-workers that are present in this application and whose disclosures form the basis for these claims were cited about 280 times by workers of ordinary skill in this art. Those workers were able to use those disclosures for their own work and arrive at new results.

It is submitted that evidence as is provided here represents a true assessment of whether the disclosures of this application are enabling for other than the specific cDNAs whose sequences are disclosed. As Kato pointed out in the before-quoted portion of his review, a worker of ordinary skill can readily prepare a cDNA of these claims even though the work to obtain them requires a great deal of effort.

That great deal of effort is not, however, undue experimentation, the test for enablement. Here, nothing approaching ingenuity beyond that expected of one of ordinary skill in this art is required, and that further ingenuity is what is meant by undue experimentation. In re Angstadt and Griffin, 190 USPQ 219, 218 (CCPM 1976).

Thus, the scope of these clams has been well enabled by the present disclosure, and this rejection should be withdrawn.

The Action has based its rejection here in part on the Board's decision in Ex Parte Maizel and has analogized the fact situation there to the present situation. It is submitted that that comparison is inapt.

The inventors in Maizel found one tree and tried to claim a forest. Dr. Sutcliffe isolated 47 clones of the claims and sequenced four of them as being illustrative. Dr. Sutcliffe planted examples of his complete claims forest. His continuing publications in this field and those of others who have used these teachings have provided growth to those plantings.

The cDNAs of these claims are more akin to the catalyst molecules of Angstadt than to the single means of Maizel. Angstadt's forty examples including one that did not work represent a smaller percentage relative to the breadth of the claims there than do the 47 isolated clones or the four clones sequenced here.

The analogy to Maizel also breaks down here because there is no analogous "means" here, stated or otherwise, as there was in Maizel. The claims do not recite biological equivalents.

The parallel with Maizel also fails because that case rested on In re Fisher, 166 USPQ 18, 24 (CCPA 1970) in which claims were drafted to a polypeptide of a length that could not have been built at the time the Fisher application was filed, as Merrifield's work on peptide synthesis had not been published. Fisher never demonstrated ability to prepare his peptide. Here all of the tools were in place and Dr. Sutcliffe and his group, and others, have been working since 1983 watering, fertilizing and growing his forest in paper after paper that details their findings with their brain-specific cDNAs. A complete set of those papers in addition to those already provided is available should the Examiner desire them. They are not included here simply to keep the file smaller.

It is thus submitted that these claims are well enabled by the application itself as well as by the unsolicited statements of others of skill in his art and by Dr. Sutcliffe's continuing work. This rejection should therefore be withdrawn.

F. Summary

Claims 29 and 31 have been amended pursuant to the Examiner's helpful suggestions. The election has been affirmed, and the non-elected claims have been cancelled. Each of the bases for rejection has been dealt with and overcome.

It is therefore submitted that this application is in condition for allowance. An early Notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
Edward P. Gamson
Reg. No. 29,381

Enclosures;
Form PTO-1449
Exhibits I and II
Documents DA, DB, DC and DD

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CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Box Non-Fee Amendments (Pats), Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on April 11, 1995.